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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,850	08/21/2002	Klaus Muehlegger	RDID01073US	5735

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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	10/019,850	MUEHLEGGER ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cov r sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-15 are pending.

2. This instant application is a 371 of PCT/EP00/04036 filed on May 5, 2000, which claims benefit of a foreign application EP 99108601. 8 filed on May 7, 1999.

3. The instant disclosure is objected because of the following informalities:

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino

acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claim 11 recites the limitation "the enzymes". There is insufficient antecedent basis for this limitation in the claim because Claim 11 is dependent on claim 1 which uses a single enzyme that is a DNA polymerase. Recitation of plurality of enzymes the in claim 11 lacks antecedent basis.

B. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the term "can", which is unclear and indefinite because it is not clear if this limitation is an actual positive step in the method or a is it a property of the DNA polymerase to incorporate the modified nucleoside triphosphates. Therefore meets and bounds of the claim 1 is unclear.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (c) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

A. Claims 1-7, 10-11, 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Ansorge et al. (WO 93/03180), (USPN. 5,912,118 is used as a English translation version of the WO 93/03180).

Ansorge et al. teach a method of claim 1, 3, 5 and 12, for enzymatic nucleic acid labeling and DNA sequencing (see column 3, lines 28-38) wherein Ansorge et al. disclose that the method uses a DNA polymerase, a nucleic acid template, a primer, and modified nucleotides which can be incorporated by polymerase into newly synthesized DNA (see column 3, lines 28-33, column 5, lines 10-19, lines 53-64) wherein one or all four natural deoxynucleoside triphosphates (dNTPs) are replaced entirely by the corresponding modified dNTPs , such that the full length nucleic acid generated comprises the all four bases carrying modified nucleotides (see column 4, lines 3-19, column 6, lines 28-35) which meets the limitation in the claims 1,3, 5, reciting atleast two or three natural nucleotides replaced by modified dNTPs;

With regard to claims 2, 4, and 6, Ansorge et al. teach that the modified nucleotides incorporated into the newly synthesized nucleic acid are detectable by nonradioactive methods (see column 2, lines 29-40);

With regard to claim 7, Ansorge, et al. teach that all four bases carrying different labels (see column 4, lines 7-19);

With regard to claim 10, Ansorge, et al. teach that the enzyme used in labeling a nucleic acid of claim 1 was a DNA polymerase (see column 5, lines 10-19);

With regard to claim 11, Ansorge et al. teach that the method uses reverse transcriptase and a DNA polymerase (see column 5, lines 10-19);

With regard to claim 13, Ansorge et al. teach that the method was used for DNA sequencing (see column 4, lines 3-13);

With regard to claim 14, Ansorge et al. teach that the method was used for highly sensitive detection or quantitation of one or several nucleic acid sequences (see column 5, lines 34-42).

Thus the disclosure of Ansorge et al. meets the limitations in the instant claims.

B. Claims 1-7, 10-11, 12-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Ansorge et al. (USPN. 5,912,118).

Ansorge et al. teach a method of claim 1, 3, 5 and 12, for enzymatic nucleic acid labeling and DNA sequencing (see column 3, lines 28-38) wherein Ansorge et al. disclose that the method uses a DNA polymerase, a nucleic acid template, a primer, and modified nucleotides which can be incorporated by polymerase into newly synthesized DNA (see column 3, lines 28-33, column 5, lines 10-19, lines 53-64) wherein one or all four natural deoxynucleoside triphosphates (dNTPs) are replaced entirely by the corresponding modified dNTPs , such that the full length nucleic acid generated comprises the all four bases carrying modified nucleotides (see column 4, lines 3-19, column 6, lines 28-35) which meets the limitation in the claims 1,3, 5, reciting atleast two or three natural nucleotides replaced by modified dNTPs;

With regard to claims 2, 4, and 6, Ansorge et al. teach that the modified nucleotides incorporated into the newly synthesized nucleic acid are detectable by nonradioactive methods (see column 2, lines 29-40);

With regard to claim 7, Ansorge, et al. teach that all four bases carrying different labels (see column 4, lines 7-19);

With regard to claim 10, Ansorge, et al. teach that the enzyme used in labeling a nucleic acid of claim 1 was a DNA polymerase (see column 5, lines 10-19);

With regard to claim 11, Ansorge et al. teach that the method uses reverse transcriptase and a DNA polymerase (see column 5, lines 10-19);

With regard to claim 13, Ansorge et al. teach that the method was used for DNA sequencing (see column 4, lines 3-13);

With regard to claim 14, Ansorge et al. teach that the method was used for highly sensitive detection or quantitation of one or several nucleic acid sequences (see column 5, lines 34-42).

Thus the disclosure of Ansorge et al. meets the limitations in the instant claims.

C. Claims 1-7, 9-10, 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Sasaki et al. (Proc.Natl.Acad.Sci., Vol. 95, pp. 3455-3460, 1998).

Sasaki et al. teach a method of claim 1, 3, 5 and 12, for enzymatic nucleic acid labeling and DNA sequencing (see page 3456, column 1, lines 17-24 of materials and methods section, column 2, lines 1-31) wherein Sasaki et al. disclose that the method uses a DNA polymerase, a nucleic acid template, a primer, and modified nucleotides which can be incorporated by polymerase into newly synthesized DNA (see page 3456, column 1, lines 17-24 of materials and methods section, column 2, lines 1-9) wherein four natural deoxynucleoside triphosphates (dNTPs) are replaced entirely by the corresponding modified dNTPs , such that the full length nucleic acid generated comprises the all four bases carrying modified nucleotides (see page 3456, column 2, lines 5-6 of paragraph 1, fig. 1) which meets the limitation in the claims 1,3, 5 reciting atleast two or three natural nucleotides replaced by modified dNTPs;

With regard to claims 2, 4, and 6, Sasaki et al. teach that the modified nucleotides incorporated into the newly synthesized nucleic acid are detectable by nonradioactive (fluorescence detection using ABI 377 DNA sequencer) methods (see page 3456, column 2, lines of 15-22 of paragraph 1);

With regard to claim 7, Sasaki, et al. teach that all four bases carrying different labels (R6G-3'-dATP, R110-3'-dGTP, TMR-3'-dUTP, ROX-3'-dCTP) (see page 3456, Fig. 1, column 2, lines 5-6 of paragraph 1);

With regard to claim 9, Sasaki, et al. teach that the amplification reaction is performed using double-stranded nucleic acid in the presence of two primers (see page 3456, column 1, lines 20-22 of materials and methods section);

With regard to claim 10, Sasaki, et al. teach that the enzyme used in labeling a nucleic acid was a DNA polymerase (see page 3456, column 1,line 23 of materials and methods section);

With regard to claim 13, Sasaki et al. teach that the method was used for DNA sequencing (see page 3456, column 2, lines 1-22 of paragraph 1);

With regard to claim 14, Sasaki et al. teach that the method was used for highly sensitive detection or quantitation of one or several nucleic acid sequences (see page 3456, column 2, lines of 15-22 of paragraph 1).

Thus the disclosure of Sasaki et al. meets the limitations in the instant claims.

D. Claims 1-6, 8-10, 12-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanton, Jr. et al. (USPN. 6,582,923).

Stanton Jr. et al. teach a method of claim 1 and 12, for enzymatic nucleic acid labeling and DNA synthesis (see column 13, lines 50-54), wherein Stanton Jr, et al. disclose that the

method uses a DNA polymerase, a nucleic acid template, a primer, and modified nucleotides which can be incorporated by polymerase into newly synthesized DNA (see column 162, lines 5-48, column 147, lines 39-64) wherein at least two natural deoxynucleoside triphosphates (dNTPs) are replaced entirely by the corresponding modified dNTPS , such that the full length nucleic acid generated comprises two of the four bases carrying modified nucleotides (see column 14, lines 44-50, column 16, lines 39-43, column 136, lines 28-34);

With regard to claim 2, Stanton Jr. et al. teach that the modified nucleotides incorporated into the newly synthesized nucleic acid are detectable by nonradioactive methods (column 17, lines 49-53);

With regard to claims 3-6, Stanton Jr. et al. teach enzymatic nucleic acid labeling performed using modified deoxynucleoside triphosphates wherein three or four natural nucleotides are replaced by modified dNTPs in the newly synthesized nucleic acid and detected by non-radioactive methods (see column 15, lines 3-62);

With regard to claim 8-9, Stanton Jr, et al. teach that one primer or two primers were used in the labeling of one nucleic acid strand or double-stranded nucleic acid respectively (see column 155, lines 65-67, column 156, lines 1-21, lines 42-65);

With regard to claim 10, Stanton Jr, et al. teach that the enzyme used in labeling a nucleic acid of claim 1 was a DNA polymerase (see column 155, lines 65-67);

With regard to claim 13, Stanton Jr, et al. teach that the method was used for DNA sequencing (see column 161, lines 30-67, column 162, lines 1-4);

With regard to claim 14, Stanton Jr, et al. teach that the method was used for highly sensitive detection or quantitation of one or several nucleic acid sequences (see column 161, lines 30-67, column 162, lines 1-33).

Thus the disclosure of Stanton Jr. et al. meets the limitations in the instant claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ansorge et al. (WO 93/03180) and in view of Bloch et al. (EP 0 863 213).

Ansorge et al. teach a method of claim 1 for enzymatic nucleic acid labeling (see page 5, paragraph 4, page 11, paragraph 3) wherein Ansorge et al. disclose that the method uses a DNA polymerase, a nucleic acid template, a primer, and modified nucleotides which can be incorporated by polymerase into newly synthesized DNA (see page 9, paragraph 3, page 11,

paragraph 1) wherein more than one or all four natural deoxynucleoside triphosphates (dNTPs) are replaced entirely by the corresponding modified dNTPs , such that the full length nucleic acid generated comprises the all four bases carrying modified nucleotides (see page 7, lines 19-30, page 12, paragraphs 1-3) which meets the limitation in the claim 1, reciting atleast two natural nucleotides replaced by modified dNTPs. However, Ansorge et al. did not teach the use of the said method for detection of specific nucleic acid sequences in situ.

Bloch et al. teach a method for in situ nucleic acid amplification, wherein Bloch et al. disclose that the method uses modified or labeled deoxynucleoside triphosphates in the process of in situ amplification (see page 4, lines 23-27, page 5, lines 15-25).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of enzymatic labeling of nucleic acid with modified dNTPs as taught by Ansorge et al. with the in situ detection method as taught by Bloch et al. to achieve an expected advantage of developing an improved and sensitive method for detecting target nucleic acid within the cells because Bloch et al. taught the advantage of using modified dNTPs in in-situ amplification reaction to enhance the detection of target nucleic acid and direct visualization and analysis of non-radioactive signals from amplification products (see page 5, lines13-25). An ordinary practitioner would have been motivated to combine the method of Ansorge et al. with the inclusion of in-situ detection of specific nucleic acid sequences as taught by Bloch et al. which would result in a sensitive and enhanced method for detecting specific target nucleic acid sequences in an intact cell.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
November 13, 2003

JEHANNE SOUAYA
PATENT EXAMINER
Jehanne Souaya
11/13/03